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ARTICLE

Twin Studies of Schizophrenia: From Bow-and-Arrow Concordances to Star Wars Mx and Functional Genomics

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Twin studies have been vital for establishing an important genetic contribution to the etiology of schizophrenia. The five newest studies since 1995 from Europe and Japan have confirmed earlier findings. They yielded probandwise concordance rates of 41–65% in monozygotic (MZ) pairs and 0–28% in dizygotic (DZ) pairs, and heritability estimates of approximately 80–85%. Twin studies are also valuable for investigating the etiological relationships between schizophrenia and other disorders, and the genetic basis of clinical heterogeneity within schizophrenia. Studies of discordant MZ pairs provide further insights into non-inherited factors that contribute to the multifactorial etiology of this disorder. More recently, twin studies have begun to be used to directly investigate molecular genetic and epigenetic processes underlying schizophrenia. Am. J. Med. Genet. (Semin. Med. Genet.) 97:12–17, 2000. © 2000 Wiley-Liss, Inc.

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INTRODUCTION

The pivotal role played by twin studies in establishing a genetic contribution to the etiology of schizophrenia has been reviewed in detail [Gottesman, 1991]. The weighted average probandwise concordance rates from European studies conducted between 1963 and 1987 are 48% for monozygotic (MZ) pairs and 17% for dizygotic (DZ) pairs. Heritability estimates for these studies range from 41–86% [Kendler, 1983]. One potential drawback of these studies is that they did not employ explicit operational diagnostic criteria. Results from reanalyzes [McGuffin et al., 1984; Farmer et al., 1987] of one study [Gottesman and Shields, 1972], and an independent Norwegian study [Onstad et al., 1991a], both of which employed operational diagnoses, produced heritability estimates toward the top end of the range found in earlier studies (83–87%: [McGuffin et al., 1984, 1994; Farmer et al., 1987]).

In the past few years, contrary to expectations that molecular genetics had driven "good old" twin studies (n = 13 from 1928–1991) out of the market place, the corpus of knowledge has been revitalized by five further twin studies of schizophrenia. Two studies were based on Scandinavian national population-based registers that had the advantages of systematic ascertainment and accurate calculation of population morbid risks; four studies employed explicit operational diagnostic criteria; and two employed biometrical model fitting [Neale and Cardon, 1992], that allowed formal comparison of hypotheses concerning whether, and to what extent, various genetic and environmental effects contribute to variation in liability to schizophrenia.

Beyond such univariate analyses, twin studies of schizophrenia have been employed to investigate the overlap between risk factors for schizophrenia and other psychotic disorders. Such information is potentially valuable for refining the classification of major psychiatric disorders, and for optimizing the definition of phenotypes in molecular genetic studies of schizophrenia. In addition, there is considerable clinical heterogeneity within the "taxon" of schizophrenia, and twin studies can help to unravel factors underlying variation in clinical profiles. A further application of schizophrenia twin studies involves focusing on discordant MZ pairs, looking for within-pair differences that may give clues to non-inherited or epigenetic risk factors, and examining the illness status of their offspring. We review the results of recent twin studies and discuss some of these non-traditional areas of investigation.

RESULTS OF RECENT TWIN STUDIES

Any apparent enthusiasm for the contribution of twins to the study of schizophrenia must be tempered by the reality that the data generated provide only some of the necessary pieces of information to solve the complexities involved; the data must converge with those generated by family and adoption

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strategies, and the other areas of investigation highlighted by the papers in this volume. The results of the most recent wave of twin studies (summarized in Table I) are consistent with earlier studies in supporting an important genetic contribution to the etiology of schizophrenia. In each study the probandwise concordance rate was more than twice as great in MZ than same-sex DZ pairs and, in the two studies that employed biometrical model fitting [Cannon et al., 1998; Cardno et al., 1999], the heritability estimates were substantial and remarkably similar despite methodological differences, notably ascertainment via population versus hospital registers, and use of clinical versus operational diagnoses.

The study of Kläning [1996] employed the population-based Danish Twin Register linked to the Danish National Psychiatric Register (inpatients only); the study complements but is independent of the earlier study by Fischer [1973]. Twins with register diagnoses of functional psychoses or personality disorders were followed up by examination of case records and interviews. There was a considerable drop-out, so that of 437 individuals initially identified from the register there were 51 probandwise pairs where the proband was interviewed and fulfilled criteria for strict or probable ICD-10 schizophrenia. Kläning is the only recent author to report opposite-gender DZ concordance rates (1/16, 6%). These were similar to the same-gender rates, but the numbers are too small to draw strong conclusions.

The study of Cannon et al. [1998] was based on the Finnish National Population Register. The population of twins comprised all same-gender pairs born between 1940 and 1957 (2495 MZ and 5378 same-gender DZ , with a further 1689 ?Z). Pairs broken by the death of one or both before 1967 were excluded. Twins with a clinical chart diagnosis of schizophrenia (according to ICD-8 or DSM III-R after 1987) were ascertained by linking with three national databases covering psychiatric inpatient or outpatient treatment, and disability pensions. The model fitting analysis suggested that 83% of the variance in liability to schizophrenia was due to additive genetic effects, with the remaining 17% due to individual-specific environmental effects. The major strength of this study was its ascertainment via population registers; its main limitation was the use of chart diagnoses with little personal contact by the authors, thereby limiting closure on the validity of diagnoses. A kappa of 0.84 was reported for a subset of 72 probands between register diagnoses and DSM-III-R diagnoses made by an interviewer.

The study of Franzek and Beckmann [1998] was based on all same-gender twins born between 1930 and 1972 who were admitted to any one of the three psychiatric hospitals in the Lower Franconia region of Bavaria, and who had a clinical diagnosis of a non-affective psychosis. These twins were interviewed to establish diagnoses according to DSM-III-R operational criteria, and diagnoses were also made based on Leonhard's classification of psychoses. Probandwise concordance rates for the 'middle of the road' diagnostic criteria of schizophrenia plus spectrum disorders (Table I) and also for strict DSM-III-R schizophrenia (MZ 11/14, 79%; DZ 2/12, 17%) were notably higher for both MZ and DZ pairs

TABLE I. 1996–1999 Twin Studies of Schizophrenia★

Authors	Country	Ascertainment	Diagnostic criteria	Number of pairs and probandwise concordance rate		Heritability estimate (95% CI)
				MZ	Same-gender DZ	
Kläning [1996]	Denmark	Population register	ICD-10	13; 7/16 (44%)	17; 2/19 (11%)	
Cannon et al. [1998][a]	Finland	Population register	Clinical (ICD-8; DSM-III-R after 1987)	67; 40/87 (46%)	186; 18/195 (9%)	83% (75, 89)
Franzek and Beckmann [1998]	Germany	Hospital admissions	DSM-III-R[b]	22; 20/31 (65%)	23; 7/25 (28%)	
Cardno et al. [1999]	UK	Hospital register	RDC	42; 20/49 (41%)	56; 3/57 (5%)	82% (71, 90)
			DSM-III-R	40; 20/47 (43%)	50; 0/50 (0%)	84% (19, 92)
			ICD-10	43; 21/50 (42%)	50; 1/58 (2%)	83% (7, 91)
Tsujita et al. [1992, 1996][c]	Japan	Hospital admissions	DSM-III-R	18; 11/22 (50%)	7; 1/7 (14%)	

★MZ, monozygotic; DZ, dizygotic.

[a]Rates used with the permission of Dr. Tyrone Cannon; 95% CI calculated by AGC.

[b]Includes schizophrenia spectrum disorders.

[c]Not yet final and used with the permission of Dr. Yuji Okazaki [1996].

than in the other recent studies. The reasons for this difference are unclear. The mean age of twins at assessment (40 years, SD 13.0, range 22–65) was similar to the study of Cardno et al. [1999] (46 years, SD 15.4, range 15–88). The ascertainment procedure via hospital admissions, however, may have led to particular selection for severe illness and concordant pairs.

The study of Cardno et al. [1999] was based on the Maudsley Hospital Twin Register, in London. The sample comprised all same-gender twins (where the co-twin lived to at least 15 years-of-age) who had inpatient or outpatient treatment for any functional psychosis between 1948 and 1993. The sample included the twins previously investigated by Gottesman and Shields [1972]. The principle operational diagnostic system was RDC, assessed on a non-hierarchical lifetime-ever basis. Thus, twins could qualify for more than one diagnosis during their lifetime. In addition, main-lifetime diagnoses were made according to DSM-III-R and ICD-10 criteria, where twins received only one diagnosis—this being the approach taken in the other twin studies of schizophrenia. The model fitting results suggested similar heritabilities for all three diagnostic approaches. The relatively wide confidence intervals for DSM-III-R and ICD-10 schizophrenia were due to the best-fitting model suggesting that genetic dominance effects entirely accounted for the heritabilities. This seemed to be an artifact of the low DZ concordance rates: adding one concordant DZ pair to the analysis resulted, in both cases, in heritabilities accounted for by additive genetic effects (for DSM-III-R $h^2 = 83\%$ (95% CI 72, 91); for ICD-10 $h^2 = 82\%$ (95% CI 71, 90). Patterns of inheritance in schizophrenia are compatible with the occurrence of some dominance or epistatic effects [Risch, 1990], but it is unlikely that a twin study of this size would be able to detect such effects reliably. The relatively low DZ concordance rates were probably due to the majority of twins still being within the risk period for schizophrenia (28.6% followed up beyond 55 years-of-age) and the reporting of strict diagnostic concordance only. The results of this study were consistent with those of Cannon et al. [1998] in suggesting that the environmental contribution to variance in liability was accounted for by individual-specific, rather than common (shared) familial effects.

The study of Tsujita et al. [1992; Okazaki Y, personal communication, April 27 1996] was based on admissions of same-gender twins to mental institutions in the Nagasaki prefecture, where probands fulfilled criteria for DSM-III-R schizophrenia, or schizophrenia spectrum disorders. The ratio of MZ to DZ pairs was greater in this study than in the European samples. Whereas the expected ratio in Caucasians is approximately 1:1, it is 2:1 in Japan, and the sample ratio does not differ significantly from this. The results reported are provisional as the study is not yet complete.

In conclusion, the pattern of probandwise concordance rates for schizophrenia are consistent across recent twin studies, using a diagnostic definition that is equivalent to definite (strict) plus probable schizophrenic psychoses in both probands and co-twins and making allowance for small sample fluctuations. The heritability estimates for schizophrenia are substantial and similar across recent studies.

COMBINED ANALYSIS

In view of the general consistency of results from the recent twin studies that employed operational diagnoses of schizophrenia, and also the newer Norwegian study [Onstad et al., 1991a: DSM-III-R criteria; probandwise concordance for MZ 15/31 (48%) and for DZ 1/28 (4%)], we performed a further model-fitting analysis based on the pooled twin data. We followed the same procedure as in our study of UK twins [Cardno et al., 1999], that was also essentially the same as that used in the Finnish study [Cannon et al., 1998]. The Mx program [Neale, 1999] was employed for the biometrical model fitting. Mx uses a maximum likelihood approach, based on a underlying liability-threshold model [Falconer, 1965; Gottesman and Shields, 1967], and the fit of each tested model is expressed as a goodness-of-fit χ^2. Five models were fitted, that differed according to which parameters were assumed to contribute to variance in liability: 1) individual-specific environmental variance only (E model); 2) common and specific environmental variance (CE model); 3) additive genetic and specific environmental variance (AE model); 4) additive genetic, common and specific environmental variance (ACE model); and 5) additive genetic, genetic dominance and specific environmental variance (ADE model). Nested models were compared using the χ^2 difference test [Neale and Cardon, 1992]. Where there was no significant difference, the best-fitting model was determined on grounds of parsimony, models with fewer parameters being preferred.

The pooled probandwise concordance rates for DSM-III-R schizophrenia (strict, plus probable where this category also used) were 57/114 (50.0%) for MZ and 4/97 (4.1%) for DZ pairs [Onstad et al., 1991a; Tsujita et al., 1992; Franzek and Beckmann, 1998; Cardno et al., 1999]. Morbid risk estimates were made in two of these studies and were very similar [0.74%: Tsujita et al., 1992; 0.75%: Cardno et al., 1999]. Model fitting was applied using the mean of these morbid risks. The AE model fitted best ($\chi^2 = 3.58$, $df = 1$, $P = 0.06$) with a heritability of 88% (95% CI 83, 92), and individual-specific environmental effects of 12% (95% CI 8, 17).

The pooled probandwise concordance rates for ICD-10 schizophrenia were 28/66 (42.4%) for MZ and 3/77 (3.9%) for DZ pairs [Kläning, 1996; Cardno et al., 1999]. The population morbid risk was estimated in one of these studies [0.84%: Cardno et al., 1999]. Based on this estimate, the AE model was best-fitting ($\chi^2 = 2.66$, $df = 1$, $P = 0.10$) with a heritability of 83% (95% CI 74, 90), and individual-specific environmental effects of 17% (95% CI 10, 26).

Thus, the results of the pooled sample analyses also support a substantial genetic contribution to variance in liability to schizophrenia, with no significant difference between the heritability estimates for schizophrenia de-

fined by DSM-III-R and ICD-10 diagnostic criteria.

RELATIONSHIPS BETWEEN SCHIZOPHRENIA AND OTHER DISORDERS

Patterns of co-aggregation, or co-morbidity, in family studies suggest a familial relationship between schizophrenia, other psychotic disorders and certain personality disorders, e.g., schizotypal personality disorder [Kendler et al., 1993]. In view of this, some twin studies have investigated a broader phenotype that has included such schizophrenia spectrum disorders. In the part of the Maudsley twin series investigated by Gottesman and Shields [1972], Farmer et al. [1987] found a maximum MZ/DZ concordance ratio for a phenotype that included DSM-III schizophrenia, affective disorder with mood incongruent delusions, atypical psychosis and schizotypal personality disorder. These results are consistent with there being a genetic basis for a phenotype that includes this range of spectrum disorders. They do not tell us, however, to what extent risk factors are shared in common between these disorders.

In the Finnish twin sample, Cannon et al. [1998] investigated whether clinically-defined schizophrenia and other psychoses lie on a single continuum of liability. This analysis was based on a liability-threshold model with multiple thresholds [Reich et al., 1972]. In this model schizophrenia and other psychoses are assumed to share the same etiological risk factors, but a higher level of liability is required for schizophrenia to be expressed than other psychotic disorders. The multiple threshold model did not fit well, suggesting that schizophrenia and other psychoses do not lie on a single liability continuum. Comparison with alternative models, however, was not performed.

In the UK twin sample, Cardno et al. [submitted] performed a more general investigation of whether RDC schizophrenia, schizoaffective disorder and mania share genetic and environmental risk factors in common, when these disorders were defined on a non-hierarchical basis that allowed within-person comorbidity between disorders. They used a correlated liability model [Neale and Kendler, 1995] to test whether the three possible pairings of these disorders had significant additive genetic and individual-specific environmental correlations, to indicate the extent that such effects were shared in common between the disorders. Significant additive genetic correlations were found for each pairing, but environmental correlations were non-significant. Analyses of all three disorders together under independent and common pathway models [Neale and Cardon, 1992] were consistent with schizophrenia and mania having both shared and diagnosis-specific genetic effects, whereas schizoaffective disorder had only genetic effects that were also shared with the other disorders.

These results are consistent with those of Cannon et al. [1998] in suggesting that schizophrenia is genetically related to other psychoses, but does not share all of its risk factors with them. The results also shed some light on the status of schizoaffective disorder, that has long been a subject of controversy [Kendell, 1988; Bertelsen and Gottesman, 1995]. Clinically, this disorder shares features with both schizophrenia and affective psychoses, and the results of this study suggest that etiologically it is also a kind of genetic interform whose genetic liability is contributed to by a combination of genetic risk factors for schizophrenia and mania. Further research in the near term investigating the diagnostic specificity of quantitative trait loci (QTLs) will permit this hypothesis to be tested at the molecular level.

CLINICAL HETEROGENEITY WITHIN SCHIZOPHRENIA

Other studies have focused on the syndrome itself and the large degree of clinical heterogeneity within schizophrenia. Classically, schizophrenia has been divided into subtypes, such as paranoid and hebephrenic schizophrenia, based on the most prominent clinical features of the illness. A number of studies have investigated the degree of familial aggregation of these subtypes within MZ pairs concordant for schizophrenia [Farmer et al., 1984; McGuffin et al., 1987; Onstad et al., 1991b]. These have been consistent in showing that the subtypes only partly breed true (i.e., show partial homotypia), with concordance rates of 73–87% versus 50% expected by chance. This suggests that they do not define genetically-distinct subforms of schizophrenia. The rate of schizophrenia of any sort in co-twins, however, tends to be greater when the proband has a hebephrenic rather than paranoid type of illness [Gottesman and Shields., 1972; Farmer et al., 1984; McGuffin et al., 1987; Onstad et al., 1991b]. It has been hypothesized on the basis of these findings that hebephrenic and paranoid schizophrenia lie on a single continuum of liability and differ quantitatively rather than qualitatively, in terms of the level of liability required for expression of the subtype—with hebephrenic schizophrenia representing a more extreme subtype than paranoid schizophrenia. To our knowledge, however, this hypothesis has not been formally tested by model fitting on twin data. It is also not known to what extent susceptibility loci for schizophrenia in fact contribute to variation in the clinical profile of schizophrenia, and to what extent the genetic contribution to this variation is due to modifying loci. This issue has been most extensively investigated for variation in age of illness onset. There is evidence of an important genetic contribution to age at onset of schizophrenia [Kendler et al., 1987; Cannon et al., 1998], and model fitting results suggest that modifying, rather than susceptibility, loci are predominantly involved [Neale et al., 1989].

STUDIES OF DISCORDANT MZ PAIRS

Studies of the offspring of discordant MZ pairs have shown that the risk of schizophrenia-like psychosis is similar in the offspring of both the affected and unaffected MZ twins [Gottesman and Bertelsen, 1989; Kringlen and Cramer, 1989]. This implies that unaffected co-

twins of affected MZ probands carry susceptibility genes for schizophrenia but have not expressed the phenotype, and that phenocopies are probably uncommon. In view of this, studies of differences between the members of discordant MZ pairs have great potential for shedding light on non-inherited or epigenetic mechanisms that contribute to the multifactorial etiology of schizophrenia.

In the field of brain imaging, affected twins show evidence of a relative reduction in cerebral volume [Noga et al., 1996; Ohara et al., 1998], in some studies specifically reduced hippocampal volume, and also 'hypofrontality' (lack of normal stimulation of cerebral blood-flow in the prefrontal cortex) [Weinberger et al., 1992]. In contrast, cerebral volume and level of the prefrontal cortex stimulation have been shown to be similar in the unaffected members of discordant MZ pairs and normal MZ twin controls [Berman et al., 1992; Noga et al., 1996; Ohara et al., 1998]. Although sample sizes for these and other discordant MZ twin studies tend to be modest, these findings are consistent with non-inherited factors having an influence on structural and functional brain changes in schizophrenia. The relative size of genetic and environmental effects, however, is not known. Other areas where differences between members of discordant MZ pairs have also been found include cognitive function [Goldberg et al., 1993, 1995], eye tracking [Litman et al., 1997], electroencephalogram (EEG) patterns [Stassen et al., 1999], obstetric complications [McNeil et al., 1994], and dermatoglyphic patterns suggestive of aberrant fetal development during the second trimester [Markow and Gottesman, 1989; Davis and Bracha, 1996]. These findings have contributed to the increasingly prevalent hypothesis that aberrant neurodevelopment leads to schizophrenia in at least a proportion of cases [Murray, 1994]. A book by Torrey et al. [1994] summarizes the data on the largest of such rare samples to date.

There is also increasing interest in the possibility that genetic or epigenetic discordance between MZ twins may predispose to phenotypic discordance. A variety of mechanisms have been implicated [Gottesman, 1997], including differential trinucleotide repeat expansion, skewed X-inactivation in females, and differential methylation of DNA [McGuffin et al., 1994; Martin et al., 1997]. The effect of differentially expanded trinucleotide repeats has been investigated by Vincent et al. [1998] at the genomic level using the repeat expansion detection (RED) technique. Neither CAG/CTG nor GAA/TTC repeat length was found to be longer in affected than unaffected MZ twins, although small differences could not be excluded. A preliminary study of DNA methylation patterns in the putative promoter region of the dopamine D_2 receptor gene has also been performed [Petronis et al., 1999], and many more studies of epigenetic mechanisms in discordant MZ pairs with schizophrenia are likely to be published in the near future.

CONCLUSIONS

Twin studies of schizophrenia highlight the importance of close collaboration between the fields of quantitative and molecular genetics to maximize the chances of unraveling the mechanisms underlying this complex disorder. Traditional twin studies have been vital for establishing that there is an important genetic contribution to the etiology of schizophrenia, as a prerequisite for gene mapping studies. Subsequent studies have, and continue to be, valuable for defining the boundaries of the phenotype, and identifying useful covariates and novel phenotypes within the clinical syndrome. Twin studies also have a valuable role in extending phenotypes beyond the clinical presentation, to include potential biological markers. More recently, twin studies have begun to directly explore molecular genetic and epigenetic phenomena in schizophrenia. Thus, in the era of functional genomics twin studies will continue to play a vital role in helping us to understand the etiological mechanisms underlying schizophrenia.

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